REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claims 1-25 are pending in this application, of which claims 4, 7, and 13-19 are withdrawn from consideration. Claims 2, 4 and 5 are canceled. Claims 1 and 20 are amended.

Claim Amendments

Claim 1 has been amended to recite a "human" patient, support for which can be found throughout the specification, for example, in [00117] (page 28).

Claim 1 has also been amended to recite an adverse drug reaction "selected from the group consisting of Stevens-Johnson syndrome and toxic epidermal necrolysis," and "wherein the drug is a carbamazepine or phenytoin." Support for the amendment can be found, for example, in original claims 2 and 5.

Claim 20 has been amended to recite "wherein said presence is used to indicate predisposition for adverse reactions to drugs," support for which can be found, for example, in [0093].

No new matter has been added by this amendment. The Examiner is hereby requested to enter the amendment.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability.

IDS of February 4, 2006

The Applicants direct the Examiner's attention to page 1 of the two page Substitute Form PTO-1449 received at the Patent Office on February 4, 2006. The reference AA (U.S. Pat. No.

6,583,139) was not initialed as having been reviewed by the Examiner. The Applicants respectfully request that the Examiner review reference AA and provide us with an updated Substitute Form PTO-1449 indicating such review.

Rejections Under 35 U.S.C. §112, Enablement (Paragraphs 3 and 4 of the Office Action)

The rejection of claims 1-3, 5, 6, 8-12 and 20-25 under 35 U.S.C. §112, first paragraph, as allegedly not enabled, is respectfully traversed for the reasons set forth below.

As amended, claim 1 is directed to a method of assessing the risk of a human patient for developing an adverse drug reaction in response to a drug, comprising determining the presence of an HLA-B allele selected from the group consisting of HLA-B* 1502, HLA-B*5801 and HLA-B*4601, wherein the presence of the HLA-B allele is indicative of a risk for an adverse drug reaction selected from the group consisting of Stevens-Johnson syndrome or toxic epidermal necrolysis, and wherein the drug is a carbamazepine or phenytoin.

Specifically, the Office Action states that the specification is enabling for a method for assessing the risk of a human Taiwanese patient for developing Stevens-Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN) in response to carbamazepine (CBZ) comprising determining the presence of an HLA-B*1502 allele, wherein the presence of the allele is indicative of an increased risk for SJS/TEN. However, the Office Action alleges that the specification does not reasonably provide enablement for assessing the risk of any other adverse reactions in response to any other drugs in any other human population or any non-human populations using any equivalent genetic marker. For the following reasons, Applicants respectfully disagree.

Applicable Patient Populations

The Office Action asserts that the specification does not provide any analysis of any non-human subjects, or any analysis of a non-Taiwanese population. Non-human subjects are not at issue, as the current claims recite a human patient. As supported by a declaration of Dr. Yuan-Tsong Chen under 37 C.F.R. §1.132, submitted herewith ("the Declaration"), the claimed invention is enabled for all human subjects.

According to Dr. Chen, the subjects analyzed in the examples of the present application were from Taiwan, Hong Kong, Mainland China, and the U.S. All of them were descendants of Han Chinese, and carry B*1502 alleles (Paragraph 7 of the Declaration). Dr. Chen also pointed out that one of the references cited by the Office Action, Lonjou et al., reports that four individuals with CBZ-induced SJS/TEN carried the HLA-B*1502 allele, and their places of birth were Vietnam, China, Cambodia, and Reunion Island, respectively. *Id.* Another two research groups from UK (Munir Pirmohamed) and Australia (Simon Mallal) also found Asian subjects developing CBZ-induced SJS/TEN carried B*1502. *Id.* Thus, Dr. Chen showed that experimental data from Asian populations, beyond Taiwanese or Chinese, demonstrate a strong association between HLA-B*1502 and CBZ- induced SJS/TEN.

The Office Action cites two references, Hung et al.[1] and Lonjou et al.[2], for the proposition that HLA-B*1502 is not indicative of an increased risk for CBZ- induced SJS/TEN in all human populations. Dr. Chen indicated that, contrary to the assertion of the Office Action, Hung et al. support the notion that HLA-B*1502 is indicative of an increased risk of SJS/TEN in different populations (Paragraph 8 of the Declaration). Dr. Chen provided two reasons:

> In Figure 2 of this reference, Hung et al. present a working model for the pathogenesis of CBZ-induced SJS/TEN. In this model, CBZ or its metabolite binds to a peptide, and the binding complex serves as a bridge between HLA-B*1502 of keratinocytes and T-cell receptors of cytotoxic T cells, causing HLA-B*1502-bearing keratinocytes to be recognized by cytotoxic T cells and inducing SJS/TEN. This model is consistent with the observation that HLA molecules are necessary for the activation of drug-specific T cells (see, *e.g.*, Hung et al., Page 232, right column, line 12, and reference 42 and 66 cited therein). Based on this model, any person having HLA-B*1502, regardless of the ethnic background, has a risk for CBZ-induced SJS/TEN. (Paragraph 8 of the Declaration)
>
> Hung et al. further teach that HLA-B*1502 allele frequency positively correlate with the prevalence of CBZ-induced SJS/TEN in different populations (page 233 of Hung et al., left column, second paragraph). For example, at page 233, last paragraph of left column to first paragraph of right column, Hung et al. teach that the allele frequency of HLA-B*1502 is only 0-0.1% in Caucasians, which may explain the apparent lower incidence

[1] Hung et al., "HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine," Personalized Medicine (2005) 2(3):225-237.
[2] Lonjou et al., "A marker for Stevens-Johnson syndrome...: ethnicity matters", Pharmacogenomics J. (2006) 1-4.

of CBZ-induced SJS in Caucasians. On the other hand, HLA-B*1502 is quite common in Malaysia, and CBZ is reported to be the major offending drug for SJS/TEN in that population. (Paragraph 9 of the Declaration)

The Office Action cites Hung et al. for teaching "alleles may be present in different frequencies in different populations, and that it is more likely to find a positive result when a study is conducted in a population with a high frequency of the allele (p.233, left col., lns. 8-13)." As pointed out by Dr. Chen, while this teaching indicates that it is less likely to find HLA-B*1502 in Caucasians, it does not mean that HLA-B*1502, once found in Caucasians, cannot be used to predict the risk for developing SJS/TEN. Therefore, this teaching does not undermine the correlation between HLA-B*1502 and SJS/TEN (Paragraph 10 of the Declaration).

The Office Action also alleges Hung et al. as teaching "as study results can vary between study populations, it remains to be seen to what extent the association between HLA-B*1502 and CBZ-induced SJS-TEN applies to other populations (p.233, right col., lns. 11-16)." According to Dr. Chen, the correct quote of the latter part should be "it remains to be seen to what extent the strong genetic association between HLA-B*1502 and CBZ-induced SJS/TEN applies to other populations" (Paragraph 11 of the Declaration, original emphasis). As discussed by Dr. Chen, the allele frequency of HLA-B*1502 varies among different populations; a person skilled in the art would recognize that if the allele frequency is low in a population, it may not be easy to obtain a statistically significant result using this population. *Id.* In other words, if it is difficult to find sufficient Caucasians with HLA-B*1502 who have taken CBZ, one cannot perform a meaningful statistical study of the association between HLA-B*1502 and CBZ-induced SJS/TEN, let alone finding a strong genetic association. However, this technical difficulty does not reduce the correlation between HLA-B*1502 and CBZ-induced SJS/TEN. *Id.*

The other reference, Lonjou et al., was cited as allegedly teaching "HLA-B*1502 is not a useful prediction marker of CBZ related SJS in the European population (p.3, left col., second paragraph)." This reference describes a preliminary study containing 12 European CBZ-induced

SJS/TEN cases. Of the 12 patients, only 4 had an HLA-B*1502, and all 4 of them had an Asian ancestry. Lonjou et al. thus concluded that the HLA-B*1502 allele is not a universal marker and that ethnicity matters. According to Dr. Chen, this statement does not contradict the claimed invention (Paragraph 12 of the Declaration). Dr. Chen explained that in the invention claimed in this application, the presence of HLA-B*1502 is used to indicate a higher risk for CBZ-induced SJS/TEN, rather than the other way around (namely predicting that CBZ-induced SJS/TEN patients should have the HLA-B*1502 allele). *Id.* The fact that HLA-B*1502 is a risk factor for CBZ-induced SJS/TEN does not rule out the possibility that other risk factors may also exist. Similarly, the existence of other risk factors does not change the fact that the presence of HLA-B*1502 is indicative of increased risk for CBZ-induced SJS/TEN. *Id.* Thus, as Dr. Chen explained, the observation of Lonjou et al. may reflect the low allele frequency of HLA-B*1502 in Europeans, but it does not render the claimed invention less predictable. *Id.*

Dr. Chen further pointed out that factors of low allele frequencies can be useful genetic markers as well (Paragraph 13 of the Declaration). For example, the American College of Medical Genetics recommended 25 alleles of CFTR gene for routine diagnostic testing for cystic fibrosis (see, e.g., Tait et al.[3], Tables 6 and 7). Most of the 25 alleles are present in very low frequencies in Caucasians (see Table 7 of Tait et al.; the alleles not listed in Table 7 are even more rare), yet they are still recommended markers. *Id.*

Thus, as concluded by Dr. Chen, the current claims are enabled to their full scope, including all human subjects (Paragraph 18 of the Declaration).

Adverse Reactions and Drugs

[3] Tait et al., "Cystic fibrosis," Gene Clinics, posted March 26, 2001 at http://www.geneclinics.org/servlet/access?db=geneclinics&id=8888889&key=hTAmeSXYiaUo1&gry=INSERTGRY&fcn=y&fw=IRVN&filename=/profiles/cf/details.html (copy attached as Exhibit 1)

The Office Action agrees that the claims are enabled with respect to CBZ-induced SJS/TEN, but it asserts that the specification contains no measure of the statistical significance for drugs other than CBZ. According to Dr. Chen, the claimed invention is applicable to at least SJS/TEN caused by CBZ or phenytoin (Paragraph 14 of the Declaration). The statistical data for phenytoin are included in Paragraph [0082] of the present specification (*Id.*) and Paragraph 15 of the Declaration. Similarly, the Office Action also states that the specification teaches that 38 of the 42 carbamazepine-induced SJS/TEN patients also had the HLA-Cw*0801 allele, without a statistical analysis of the significance. The Declaration provides the requested statistical analysis in Paragraph 16.

The Office Action further states that the specification does not provide any statistical analysis of the linkage between HLA-B*1502 and HLA-Cw*0801. It is well known in the art that HLA-B*1502 has a strong linkage disequilibrium with HLA-Cw*0801 (see, e.g., http://www.ncbi.nlm.nih.gov/projects/mhc/ihwg.fcgi). In Dr. Chen's opinion, this public information, when coupled with our data that HLA-B*1502 is associated with CBZ or phenytoin-induced SJS/TEN, would immediately lead a person skilled in the art to recognize that HLA-Cw*0801 is associated with the same medical conditions (Paragraph 17 of the Declaration).

In summary, according to Dr. Chen, the current claims are enabled to their full scope, including the use of HLA-B*1502 as an indicator of risk for CBZ or phenytoin-induced SJS/TEN in all human subjects who have HLA-B*1502 (Paragraph 18 of the Declaration). It should be noted that the CBZ and phenytoin in the claimed invention encompass their metabolites and analogs that have the same therapeutic applications as CBZ and phenytoin, respectively. The efficacy or dosage of each of these metabolites or analogs may be different from that of CBZ and phenytoin. However, to the extent the metabolite or analog can induce SJS or TEN, a method is enabled by the present application to assess the risk for such SJS/TEN, based on the presence of, e.g., HLA-B*1502.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §102 (Paragraphs 5 and 6 of the Office Action)

The rejection of claims 20, 21, 23 and 25 under 35 U.S.C. §102 as allegedly unpatentable in view of Trachtenberg (U.S. Patent No. 5,550,039) is respectfully traversed for the reasons set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

As amended, claim 20 is directed to a method of pharmacogenomics profiling for a human patient comprising determining the presence of at least one HLA-B allele selected from the group consisting of HLA-B*1502, HLA-B*5801, and HLA-B*4601, wherein said presence is used to indicate predisposition for adverse reactions to drugs. Trachtenberg does not disclose or suggest that any gene or allele can be used to indicate predisposition for adverse reactions to drugs, let alone HLA-B*1502, HLA-B*5801, or HLA-B*4601. Rather, Trachtenberg discloses that his "HLA-B genotyping system will be valuable in typing potential transplantation donors, where very precise HLA matching appears to be critical in minimizing risk of graft versus host disease." U.S. 5,550,039, Col. 14, lines 53-57. Therefore, the cited reference does not disclose or suggest each and every element of claim 20. Claim 21, 23 and 25 depend from claim 20 and recite additional elements that further distinguish them from Trachtenberg. Since Trachtenberg does not disclose or suggest each and every element of claim 20, it also cannot teach each and every element of claim 21, 23 or 25.

Accordingly, the standard of anticipation is not met, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103 (Paragraphs 7 and 8 of the Office Action)

The rejection of claims 22 and 24 under 35 U.S.C. §103 as allegedly unpatentable over Trachtenberg (U.S. Patent No. 5,550,039) in view of Yates et al. (1997) is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

Claim 22, which depends from claim 20, further comprises determining the presence of at least one genetic factor selected from the group consisting of thiopurine methyltransferase and the genes for the long-QT syndrome. Claim 20, in turn, is directed to a method of pharmacogenomics profiling for a human patient comprising determining the presence of at least one HLA-B allele selected from the group consisting of HLA-B*1502, HLA-B*5801, and HLA-B*4601, wherein said presence is used to indicate predisposition for adverse reactions to drugs. As discussed above, Trachtenberg does not disclose or suggest that any gene or allele can be used to indicate predisposition for adverse reactions to drug. Yates et al. does not cure this deficiency in Trachtenberg. Rather, Yates et al. discloses "a method with which to diagnose patients with TPMT deficiency or heterozygosity at the TPMT gene locus." Yates et al., p. 612, second column, second ¶ (lines 6-9). Since neither Trachtenberg nor Yates et al. disclose or suggest the combination of all the elements of claim 22, the requirement under 35 U.S.C. §103 is not satisfied.

Claim 24, which also depends from claim 20, recites wherein the presence of the allele is determined by using DNA prepared from the peripheral blood of the patient. Claim 20, in turn, is directed to a method of pharmacogenomics profiling for a human patient comprising determining the presence of at least one HLA-B allele selected from the group consisting of HLA-B*1502, HLA-B*5801, and HLA-B*4601, wherein said presence is used to indicate predisposition for adverse reactions to drugs. Similar to that discussed above, Trachtenberg does

not disclose or suggest that any gene or allele can be used to indicate predisposition for adverse reaction to drugs. Also similar to that discussed above, Yates et al. does not make up for this deficiency. Since neither Trachtenberg nor Yates et al. disclose or suggest the combination of all the elements of claim 24, the requirement under 35 U.S.C. §103 is not satisfied.

Thus, withdrawal of this rejection is respectfully requested.

Conclusions

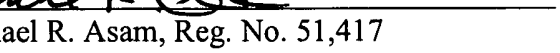
For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at 404-892-5005.

Enclosed with this Amendment is a Petition for One-Month Extension of Time. Please apply the $60.00 fee for the Petition for One-Month Extension of Time (small entity) as well as any other applicable fees, charges, or credits to deposit account 06-1050.

Respectfully submitted,

Date: 9-18-06



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